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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Antidepressant Compositions comprising Phenoxyalkylamines

We, SMITH KLINE & FRENCH LABORATORIES of 1500 Spring Garden Street, City of Philadelphia, Zone 1, Commonwealth of Pennsylvania, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to antidepressant compositions which are unexpectedly useful in the treatment of a wide range of mild to severe depressive disorders.

The novel compositions of this invention have a pharmacological profile strikingly similar to that of imipramine, a known antidepressant, but comprise as the active ingredient a compound of unrelated chemical structure. A prominent pharmacological property of these compositions is their ability to prevent reserpine-induced ptosis in rats. This pharmacological procedure is especially useful to characterize the antidepressant activity of imipramine.

Unlike other antidepressants, the compositions of this invention do not inhibit monoamine oxidase activity *in vivo*. These compositions are further characterized by relative freedom from side effects, a rapid onset of action and effectiveness in both mild and severe depression

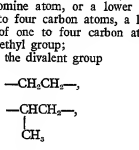
More specifically the antidepressant compositions of this invention comprise in dosage unit form a nontoxic pharmaceutical carrier and a phenoxyalkylamine of the following general formula:

I

in which:

R and R_1 each represent a hydrogen, chlorine or bromine atom, or a lower alkyl group of one to four carbon atoms, a lower alkoxy group of one to four carbon atoms, or a trifluoromethyl group;

X represents the divalent group



R_2 represents a hydrogen atom or a methyl group; and

R_3 represents a methyl group or, when taken together with R_2, forms with the nitrogen to which they are attached a pyrrolidine or piperidine ring.

A preferred composition in accordance with this invention comprises the compound N,N - dimethyl - 2 - (2,6 - dichlorophenoxy)propylamine.

The nontoxic pharmaceutically acceptable acid addition salts of the compounds of the above formula are also included within the scope of this invention since such salts are likewise effective for producing antidepressant activity. Both organic and inorganic acids can be employed to form pharmaceutically acceptable salts, illustrative acids being sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, ethanedisulfonic, sulfamic, succinic, fumaric, maleic and benzoic acids. These salts are prepared by methods known to the art.

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The pharmaceutical compositions of this invention comprise a phenoxyalkylamine of formula I in an amount sufficient to produce antidepressant activity. Preferably the compositions contain from 10 mg. to 500 mg. of medicament, advantageously from 25 mg. to 400 mg. per dosage unit.

The pharmaceutical carrier employed in the composition can be either a solid or liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar pectin and acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly the carrier or diluent may include a time delay material such as glyceryl monostearate or glycerol distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed and are prepared by methods well known to the art. Thus if a solid carrier is used the composition can be tabletted, used as a pharmaceutical powder, placed in a hard gelatin capsule or put up in the form of a troch or lozenge. If a liquid carrier is used the composition can be in the form of a soft gelatin capsule or a liquid suspension. Parenteral dosage forms are obtained by dissolving a water-soluble salt of the active medicament in sterile, pyrogen free water or saline solution in a concentration such that 1 cc. of the solution contains from about 10 mg. to about 50 mg. of active medicament. The solution can then be filled into single or multiple dose ampules.

As used herein the term dosage unit signifies a physically discrete unit containing an individual quantity of the active component in association with a pharmaceutical diluent or carrier, the quantity of active compound being such that one or more units are required for a single therapeutic administration. It does not include mere solutions in water or other common solvent except when such are packaged in ingestible containers or have been prepared so as to be acceptable for parenteral injection.

The compositions of the invention may be administered to treat both mild and severe depression as exhibited by mild depressed outpatients and more severely disturbed and hospitalized depressed patients, respectively. The active medicament in dosage units as described above may be administered orally or parenterally in repeated doses in a range of from 10 mg. to 1500 mg. daily. In mild depression, the daily dosage is from 10 mg. to 250 mg. of active medicament, advantageously from 25 mg. to 250 mg. In severe depression, the daily dosage is from 250 mg. to 1500 mg. of active medicament, advantageously from 250 mg. to 1200 mg.

The compounds of Formula I above which form the active medicament in the pharmaceutical compositions of this invention are prepared by the following general procedure. The appropriate phenol (as the sodium salt) is condensed with the aminoalkyl halide to give the product directly or alternatively condensed with an α-haloaminoalkylamide and the resultant phenoxyamide reduced with for example lithium aluminum hydride to the alkylamine.

The following examples are not limiting but set forth in more detail the preparative procedures for the compounds of Formula I and illustrate specific pharmaceutical compositions of this invention.

EXAMPLE 1

To a suspension of 1.9 g. of sodium hydride in 50 ml. of dry toluene is rapidly added a solution of 8.8 g. of 2,6-dimethylphenol in 60 ml. of dry toluene. The mixture is stirred at reflux for one hour, then cooled in an ice bath while a solution of 15 g. of N,N - dimethyl - α - bromopropionamide (prepared from the reaction of α-bromopropionyl bromide and dimethylamine) is added. The mixture is stirred at reflux for 12 hours and then filtered. The filtrate is washed with 10 percent sodium hydroxide solution and then with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is distilled at 110—123° C./0.6—0.8 mm. to give N,N - dimethyl - α - (2,6 - dimethylphenoxy)propionamide.

To a stirred suspension of 11.7 g. of lithium aluminum hydride in 250 ml. of dry ether is added a solution of 25.3 g. of N,N 1 dimethyl - α - (2,6 - dimethylphenoxy)-propionamide in 250 ml. of dry ether. During the addition the exothermic reaction warms the mixture to reflux and an additional 300 ml. of ether is added. The mixture is stirred at reflux for two and one-half hours and then at room temperature for 61 hours. A solution of 24.3 ml. of ethyl acetate in 50 ml. of ether is added during 15 minutes, followed by 22.5 ml. of water during 20 minutes. The mixture is stirred at room temperature for one hour and filtered. The filtrate is dried over sodium sulfate and concentrated. The residue is distilled at 70—74° C./0.3 mm. to give N,N - dimethyl - 2 - (2,6 - dimethylphenoxy)propylamine.

To a sample of the amine in ether is added ethereal hydrochloric acid to form the hydrochloride salt. Recrystallization from absolute ethanol-ether and then isopropanol-ether yields the N,N - dimethyl-2 - (2,6 - dimethylphenoxy)propylamine hydrochloride, m.p. 161.5—162.5° C.

EXAMPLE 2

Using the same procedure as in Example 1, 2.6 g. of sodium hydride, 16.3 g. of 2,6-dichlorophenol and 21.1 g. of N,N-dimethyl-

α-bromopropionamide are reacted to yield N,N - dimethyl - α - (2,6-dichlorophenoxy)-propionamide.

Similarly, 6.25 g. of lithium aluminum hydride and 17.6 g. of N,N - dimethyl - α-(2,6 - dichlorophenoxy)propionamide are refluxed together for 22 hours to yield N,N-dimethyl - 2 - (2,6 - dichlorophenoxy)propylamine.

Ethereal hydrochloric acid is added to a solution of a sample of this amine in ether to form the hydrochloride salt. Recrystallization from isopropanol-ether yields N,N-dimethyl - 2 - (2,6 - dichlorophenoxy)propylamine hydrochloride, m.p. 175.5—177.5° C.

EXAMPLE 3

A solution of 22.5 g. of anhydrous dimethylamine in 26.3 g. of formic acid and 50 g. of 2,6 - dichlorophenoxyacetone (prepared from the reaction of 2,6-dichlorophenol and chloroacetone) is heated at a reaction temperature of 120—125° C. until the evolution of carbon dioxide almost ceases. The mixture is cooled to room temperature and made acidic with dilute hydrochloric acid. The aqueous layer is separated, washed with ether, made alkaline with 40% sodium hydroxide and the amine taken up with ether. After drying over potassium carbonate the ether is removed by evaporation and the oily residue is distilled at 90—91° C./0.25 mm. to give a yellow oil, 2-(2,6-dichlorophenoxy) - N,N,1 - trimethylethylamine.

A sample of this amine in ether is treated with anhydrous hydrochloric acid, and the colorless hydrochloride salt is collected and recrystallized from alcohol-ether, then isopropanol, to give white crystals, m.p. 196—197° C.

EXAMPLE 4

A dry toluene solution of β-dimethylaminoethyl chloride is prepared by trituration of 144.1 g. of the amine hydrochloride in toluene with a large excess of potassium hydroxide pellets.

2,6-Dichlorophenol (81.5 g.) in 300 ml. of dry toluene is added slowly to a stirred suspension of 12.5 g. of sodium hydride in 200 ml. of toluene over a period of 20 minutes. The mixture is stirred at reflux for one hour and cooled. The toluene solution of β-dimethylaminoethyl chloride is added dropwise over a period of one hour and the well-stirred mixture is refluxed for eight hours. After cooling to room temperature the mixture is treated with 150 ml. of water followed by 250 ml. of 3M hydrochloric acid. The toluene layer is separated and extracted with 250 ml. of 3M hydrochloric acid. The combined aqueous acid solution is extracted with ether and then made basic with 40% sodium hydroxide. The amine is taken up with ether and the aqueous layer is extracted several times with ether. The combined ether solution is extracted once with water, dried over potassium carbonate, and evaporated. The amber residue is distilled at 90—92° C./0.8—0.9 mm. to give N,N - dimethyl - 2 - (2,6 - dichlorophenoxy)-ethylamine.

A sample of N,N - dimethyl - 2 - (2,6-dichlorophenoxy) - ethylamine in 50 ml. of absolute ether is treated with anhydrous hydrochloric acid until the mixture is acidic. The solid is collected by filtration and is recrystallized from absolute ethanol-ether to give the hydrochloride salt, m.p. 172—174° C.

EXAMPLE 5

To a stirred suspension of 2.9 g. of sodium hydride in 75 ml. of sodium-dried toluene is added a solution of 13.6 g. of 2,6-dimethylphenol in 100 ml. of dry toluene over a 20 minute period. The mixture is stirred at reflux for one hour and cooled. A toluene solution of 3 - dimethylaminopropylchloride, which is prepared by triturating 35.4 g. of 3-dimethylaminopropylchloride hydrochloride with an excess of potassium hydroxide pellets under toluene, is added over a one hour period. Reflux is resumed and continued for eight hours. After the mixture is cooled, 50 ml. of water and 75 ml. of 3N hydrochloric acid are added. The toluene layer is separated and extracted with 75 ml. of 3N hydrochloric acid. The combined aqueous extract is washed with ether, made basic with 40% sodium hydroxide and extracted with ether. The ether solution is washed with water, dried over potassium carbonate and concentrated. The residue is distilled to give a colorless oil, N,N-dimethyl-3-(2,6-dimethylphenoxy)propylamine, b.p. 104—107° C./0.5—0.75 mm.

Anhydrous hydrogen chloride is bubbled into an ether solution of a sample of this amine. The white precipitate which forms is recrystallized from ethanol-ether to yield the hydrochloride salt, m.p. 170—172° C.

EXAMPLE 6

To a stirred suspension of 4.7 g. of sodium hydride in 110 ml. of sodium-dried toluene is added a solution of 25.1 g. of 2,4-dichlorophenol in 180 ml. of dry toluene over a 15 minute period. The mixture is stirred at reflux for 55 minutes, then cooled in an ice bath during the 15 minute addition of a toluene solution of β-dimethylaminoethyl chloride, prepared by triturating 46 g. of β-dimethylaminoethyl chloride hydrochloride with potassium hydroxide pellets under toluene. After an eight hour period of stirring at reflux the mixture is cooled and 50 ml. of water and 80 ml. of 3N hydrochloric acid are added. The toluene layer is separated and washed with 3N hydrochloric acid. The combined acid extract is washed

with ether, made basic with 40 percent sodium hydroxide solution and extracted with ether. The ether extract is washed with distilled water, dried over sodium sulfate and concentrated. Fractional distillation of the residue yields a light yellow oil, N,N-dimethyl - 2 - (2,4 - dichlorophenoxy)ethylamine, b.p. 94—107° C./.35 mm.

Ethereal hydrochloric acid is added to a solution of a sample of this amine in ether. The resulting solid is recrystallized from isopropanol-ether to yield the hydrochloride salt, m.p. 125.5—127.5° C.

EXAMPLE 7

To a stirred suspension of 7.5 g. of sodium hydride in 350 ml. of sodium-dried toluene is added a solution of 50 g. of 2,6-diisopropylphenol in 200 ml. of dried toluene over a 30 minute period. The mixture is stirred for one hour at 25° C. and for 70 minutes at reflux temperature. To the cooled mixture is added a toluene solution of β-dimethylaminoethyl chloride (prepared by triturating 140 g. of β-dimethylaminoethyl chloride hydrochloride with excess potassium hydroxide pellets under toluene) during a 20 minute period. Reflux is resumed and continued for 12 hours. To the cooled, stirred mixture is added 100 ml. of water and 160 ml. of 3N hydrochloric acid. The toluene layer is separated and washed with 3N hydrochloric acid. This acidic aqueous solution is washed with ether, made basic with excess 40% sodium hydroxide solution and extracted with ether. The ether extract is washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated. Vacuum distillation of the residue gives a colorless oil, N,N-dimethyl - 2 - (2,6 - diisopropylphenoxy)ethylamine, b.p. 84—88° C./.3 mm.

Anhydrous hydrogen chloride is bubbled into an ethereal solution of a sample of this amine until the mixture is acidic. The hydrochloride salt formed is recrystallized from isopropanol-ether, m.p. 207—210.5° C.

EXAMPLE 8

To a stirred suspension of 2.9 g. of sodium hydride in 70 ml. of sodium-dried toluene is added a solution of 25.2 g. of 2,6-dibromophenol in 70 ml. of dry toluene over a 10 minute period. The mixture is stirred at reflux temperature for 55 minutes, then cooled in an ice bath while a toluene solution of β-dimethylaminoethyl chloride, which had been prepared by triturating 28.8 g. of β - dimethylaminoethyl chloride hydrochloride with potassium hydroxide pellets under toluene, is added over a 15 minute period. This mixture is stirred at reflux for eight hours, then cooled to room temperature. After addition of 30 ml. of distilled water and 50 ml. of 3N hydrochloric acid, the toluene layer is separated and washed with 50 and 20 ml. portions of 3N hydrochloric acid. The combined acid solution is washed with ether, made basic with 40 percent sodium hydroxide solution and extracted with ether. The ether extract is washed with distilled water, dried over potassium carbonate and concentrated. Fractional distillation of the residue yields a light yellow oil, N,N - dimethyl - 2 - (2,6 - dibromophenoxy)ethylamine, b.p. 106—116° C./.35—.60 mm.

Ethereal hydrochloric acid is added to an ethereal solution of a sample of this oil. The hydrochloride salt is recrystallized from isopropanol-ether to give white crystals, m.p. 201—203.5° C.

EXAMPLE 9

Following the general procedure of Example 4, the sodium 2,6-dichlorophenoxide (18.5 g.) prepared from sodium hydride and 2,6-dichlorophenol is reacted with 20.4 g. of N - (β - chloroethyl)pyrrolidine freshly liberated in toluene to give upon workup an oily residue which is distilled to give N[2 - (2,6 - dichlorophenoxy)ethyl] pyrrolidine, b.p. 118—122° C./0.15 mm.; hydrochloride salt, m.p. 181.5—182.5° C.

EXAMPLE 10

Similarly following the general procedure of Example 4, the sodium 2,6-dichlorophenoxide (18.5 g.) prepared from sodium hydride and 2,6-dichlorophenol is reacted with 22.3 g. of N - (β - chloroethyl)piperidine freshly liberated in toluene to give upon workup an oily residue which is distilled to give N - [2 - (2,6 - dichlorophenoxy)ethyl] piperidine, b.p. 121—124° C./0.15 mm.; hydrochloride salt, m.p. 185—186° C.

EXAMPLE 11

A solution of 18.9 g. of N,N-dimethyl-2 - (2,6 - dichlorophenoxy)propylamine (prepared as in Example 2) in 75 ml. of benzene is added over a two hour period to a solution of 12.1 g. of cyanogen bromide in 100 ml. of benzene, at 50—55° C. The reaction mixture is heated at this temperature for two hours and then allowed to stand for 18 hours. The solution is extracted with dilute hydrochloric acid and then washed with water. The benzene is removed *in vacuo* and the residue is hydrolyzed for 24 hours with 14.6 g. of sodium hydroxide and 175 ml. of 65% ethanol. The solvents are removed *in vacuo*, toluene is added and then extracted with dilute hydrochloric acid. The acid extract is basified, extracted with ether and the dried ether extract is subsequently evaporated. The residue is distilled to give N - monomethyl - 2 - (2,6 - dichlorophenoxy)propylamine, b.p. 96—116° C./.15 mm. The hydrochloride salt after recrystallization from ethanol/ether melted at 156—157° C.

EXAMPLE 12

To the sodium alkoxide formed with 2.54 g. of sodium and 9.8 g. of N,N-dimethylaminoethanol in 60 ml. of N,N - dimethylaminoethanol is added 22.0 g. of o-trifluoromethylbromobenzene and the mixture is refluxed for about 20 hours. The reaction mixture is filtered and the excess aminoalcohol removed. Ether is added and then extracted with dilute hydrochloric acid. The acidic extract is made basic, saturated with potassium carbonate solution and extracted with ether which gives a residual oil, N,N-dimethyl - 2 - (2 - trifluoromethylphenoxy)-ethylamine, b.p. 122—124° C./22 mm. The styphnate salt melts at 188—188.5° C.

EXAMPLE 13

Following the general procedure of Example 4, the sodium 3,5-bistrifluoromethylphenoxide prepared from 12.0 g. of 3,5-bistrifluoromethylphenol and 2.6 g. of sodium hydride is reacted with 8.45 g. of N,N-dimethylaminoethyl chloride in 300 ml. of toluene. Working up the reaction mixture yields N,N - dimethyl - 2 - (3,5 - bistrifluoromethylphenoxy)ethylamine, b.p. 110° C./21 mm. The hydrochloride salt recrystallized from acetone melts at 193—193.5° C.

EXAMPLE 14

To a stirred suspension of 8.4 g. of sodium hydride in 300 ml. of anhydrous toluene is added a solution of 50 g. of 2,6-dimethoxyphenol in 200 ml. of anhydrous toluene and the mixture is stirred and refluxed for two and one-half hours. The reaction mixture cooled in an ice-bath is treated slowly with N,N - dimethylaminoethyl chloride freshly liberated from 144 g. of its hydrochloride with potasssium hydroxide pellets under toluene. Refluxing is resumed for 12 hours and then the reaction mixture is cooled in an ice-bath while 100 ml. of water and 85 ml. of 12N hydrochloric acid are added. The separated toluene layer is acid washed and the combined acid extract is washed with ether, made basic with excess 40% sodium hydroxide solution and extracted with ether. The ether extract is washed with saturated sodium chloride solution, dried and concentrated. Fractional distillation of the residue yields N,N - dimethyl - 2 - (2,6-dimethoxyphenoxy)ethylamine, b.p. 107—115° C./0.7—0.85 mm. Hydrochloride salt, m.p. 186.5—187.5° C.

EXAMPLE 15

To a mixture of 26.6 g. of lithium aluminum hydride in 700 ml. of ether is added over a period of one hour a solution of 80 g. of N,N - dimethyl - α - (2 - chloro)-phenoxypropionamide. The resulting mixture is stirred for two days at room temperature and the excess hydride destroyed by careful addition of 25 ml. of water, 50 ml. of 10% sodium hydroxide solution and 25 ml. of water. The mixture is stirred for one hour and filtered. The dried ethereal filtrate is evaporated and the residue distilled *in vacuo* to give N,N - dimethyl - 2-(2-chlorophenoxy)propylamine, b.p. 75° C./1.0 mm. Hydrochloride salt, m.p. 134.5—136° C.

EXAMPLE 16

To a mixture of 19.7 g. of lithium aluminum hydride in 700 ml. of ether is added a solution of 50 g. of N,N - dimethyl - 2-phenoxypropionamide in two liters of ether over a period of one hour. The resulting mixture is stirred at room temperature for three days and then treated cautiously with 25 ml. of water, 50 ml. of 10% sodium hydride solution and 25 ml. of water. This mixture is stirred for one hour, filtered and the dried filtrate evaporated. The residue is distilled *in vacuo* to give N,N-dimethyl-2 - phenoxypropylamine, b.p. 54—59° C./0.5—0.6 mm. hydrochloride salt, m.p. 146—147° C.

EXAMPLE 17

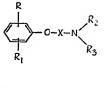
Various strength capsules are prepared containing N,N - dimethyl - 2 - (2,6 - dichlorophenoxy)propylamine either as the free base or an equivalent amount of a nontoxic pharmaceutically acceptable acid addition salt thereof from the following ingredients:

Medicament	Lactose	Magnesium Stearate
10 mg.	330 mg.	2.0 mg.
25 mg.	310 mg.	2.0 mg.
50 mg.	255 mg.	3.0 mg.
100 mg.	115 mg.	3.0 mg.

The above ingredients are screened, mixed and filled into No. 2 hard gelatin capsules.

WHAT WE CLAIM IS:—

1. A pharmaceutncal composition having anti-depressant activity, in dosage unit form, comprising a pharmaceutical carrier and as an essential active ingredient a phenoxyalkylamine or a nontoxic pharmaceutically acceptable acid addition salt thereof, said phenoxyalkylamine having the following structural formula:



in which:

R and R_1 are each a hydrogen, chlorine or bromine atom, or a lower alkyl group of from one to four carbon atoms, a lower alkoxy group of from one to four carbon atoms, or a trifluoromethyl group;

X is a divalent alkylene group having the formula

$$-CH_2CH_2-,$$

$$-CHCH_2-, \quad (CH_3 \text{ on } CH)$$

$$-CH_2CH- \text{ or} \quad (CH_3 \text{ on } CH)$$

$$-CH_2CH_2CH_2-;$$

R_2 is a hydrogen atom or a methyl group; and

R_3 is a methyl group or, when taken together with R_2 and the nitrogen to which they are attached, a pyrrolidine or a piperidine ring.

2. A pharmaceutical composition having anti-depressant activity, in dosage unit form, comprising a pharmaceutical carrier and N,N - dimethyl - 2 -(2,6 - dichlorophenoxy)-propylamine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

3. A pharmaceutical composition according to Claim 1, wherein each dosage unit contains from 10 mg. to 500 mg. of the active ingredient.

4. A pharmaceutical composition according to Claim 3, wherein each dosage unit contains from 25 mg. to 400 mg. of the active ingredient.

5. A pharmaceutical composition having anti-depressant activity, in dosage unit form, comprising a pharmaceutical carrrier and from 10 mg. to 500 mg. of N,N-dimethyl-2-(2,6-dichlorophenoxy) - propylamine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

6. A pharmaceutical composition having anti-depressant activity, in dosage unit form, comprising a pharmaceutical carrier and from 25 mg to 400 mg. of N,N - dimethyl - 2-(2,6 - dichlorophenoxy) - propylamine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

7. A pharmaceutical composition having antidepressant activity, substantially as hereinbefore described in Example 17.

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